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Effect of Daily Glucose Fluctuation on Coronary Plaque Vulnerability in Patients Pre-Treated With Lipid-Lowering Therapy

A Prospective Observational Study

Masaru Kuroda, MD,* Toshiro Shinke, MD,* Kazuhiko Sakaguchi, MD,† Hiromasa Otake, MD,* Tomofumi Takaya, MD,* Yushi Hirota, MD,† Daisuke Sugiyama, MD,‡ Masayuki Nakagawa, MD,* Hirotoshi Hariki, MD,* Takumi Inoue, MD,* Tsuyoshi Osue, MD,* Yu Taniguchi, MD,* Masamichi Iwasaki, MD,* Ryo Nishio, MD,* Hiroto Kinutani, MD,* Akihide Konishi, MD,* Noritoshi Hiranuma, MD,* Hachidai Takahashi, MD,* Daisuke Terashita, MD,* Ken-ichi Hirata, MD*

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CME Objective for This Article: At the completion of this article, the learner should be able to: 1) define the mean amplitude of glycemic excursion (MAGE); and 2) discuss the association between glycemic control and plaque vulnerability.

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From the *Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Hyogo, Japan; †Division of Diabetes and Metabolism, Department of Internal Medicine, Kobe University Graduate School of Medicine, Hyogo, Japan; and the ‡Department of Preventive Medicine and Public Health, School of Medicine, Keio University, Tokyo, Japan. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABSTRACT

OBJECTIVES This study sought to investigate the effect of daily glucose fluctuation on coronary plaque properties in patients with coronary artery disease (CAD) pre-treated with lipid-lowering therapy.

BACKGROUND There is growing evidence that glucose fluctuation, as a residual risk apart from dyslipidemia, is an important factor contributing to the development of CAD.

METHODS This prospective study enrolled 70 consecutive CAD patients who were referred for percutaneous coronary intervention and whose low-density lipoprotein cholesterol level was <120 mg/dl under statin treatment or <100 mg/dl without statins. Daily glucose fluctuation was analyzed by measuring the mean amplitude of glycemic excursion (MAGE). The plaque properties in the culprit and nonculprit lesions were assessed by virtual histology intravascular ultrasound, and the volume percentage of necrotic core within the plaque (%NC) and the presence of thin-cap fibroatheroma were evaluated.

RESULTS In total, 165 lesions were evaluated in 70 patients (40 diabetic and 30 nondiabetic patients). %NC was well correlated with MAGE ($r = 0.490$, $p < 0.001$). A linear mixed effect model showed that MAGE had the strongest effect on %NC (coefficient $\beta = 0.080 \pm 0.020$ [standard error], $p < 0.001$). The generalized linear mixed effect model revealed that MAGE was the only independent predictor of the presence of thin-cap fibroatheroma (odds ratio: 1.037; 95% confidence interval: 1.010 to 1.065; $p = 0.007$).

CONCLUSIONS Daily glucose fluctuation may have an effect on coronary plaque vulnerability in patients with CAD pre-treated with lipid-lowering therapy. Further investigations should address the rationale for the early detection and control of glucose fluctuation in the era of universal statin use for CAD patients. (J Am Coll Cardiol Intv 2015;8:800–11)

Solid evidence has accumulated to show that intervention against dyslipidemia can prevent coronary artery disease (CAD), and statin administration is now widely used for both primary and secondary prevention of CAD. However, the reduction of risk of CAD by statins has been reported to be only 30% (1), and the target level of plasma low-density lipoprotein (LDL) cholesterol is still controversial (2). Thus, there has been a focus on further managing the residual risk apart from dyslipidemia. Meanwhile, the number of patients with diabetes mellitus (DM) has been greatly increasing worldwide, and the clinical effect of abnormal glucose metabolism has been recognized in the management of CAD.

There is increasing evidence that the post-prandial blood glucose state is an important contributing factor to the development of atherosclerosis (3,4). The STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) trial revealed that a poor post-prandial state accelerates atherosclerosis, whereas improving it prevents atherosclerosis progression. It has long been recognized that glucose levels measured by a 2-h post-oral glucose tolerance test (OGTT) are strongly associated with mortality and cardiovascular disease (5,6). The DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study reported that high blood glucose concentrations 2 h after OGTT were associated with an increased risk of death that was independent of fasting blood glucose (5). However, whether glucose fluctuation may affect the coronary plaque properties in CAD patients pre-treated with lipid-lowering therapy remains largely unknown.

Virtual histology (VH) intravascular ultrasound (IVUS), which uses amplitude and frequency analysis

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CGM = continuous glucose monitoring

DM = diabetes mellitus

IGT = impaired glucose tolerance

LDL = low-density lipoprotein

MAGE = mean amplitude of glycemic excursion

PCI = percutaneous coronary intervention

TCFA = thin-cap fibroatheroma

VH-IVUS = virtual histology intravascular ultrasound

%NC = volume percentage of necrotic core within the plaque

of the IVUS backscatter signals, can reliably identify atherosclerotic plaque components (7). Reconstructed color-coded tissue maps with 4 different types of atherosclerotic plaque have high in-vitro predictive accuracy (8,9). This imaging modality enables us to characterize the coronary plaque component. The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study confirmed the clinical effect of shallow necrotic cores. In a follow-up of about 700 patients with acute coronary syndrome (ACS) by VH-IVUS examination, the presence of necrotic core adjacent to lumen, which is called thin-cap fibroatheroma (TCFA), emerged as 1 of the most significant independent predictors of future coronary events in nontreated lesions (10).

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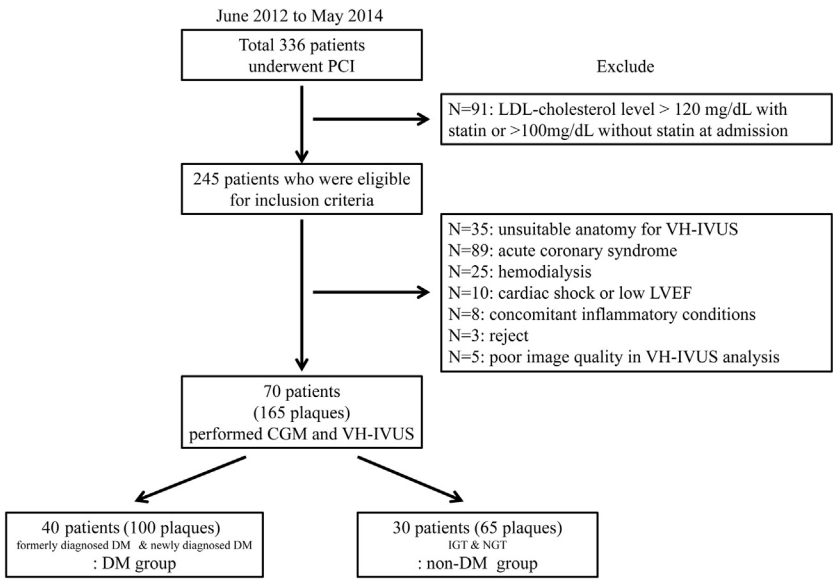
As continuous glucose monitoring (CGM) has recently become available to evaluate daily glucose fluctuation in clinical practice, we investigated the relationship between glucose fluctuation and coronary plaque properties as analyzed by CGM and VH-IVUS.

METHODS

PATIENT POPULATION. Seventy consecutive patients who had undergone percutaneous coronary intervention (PCI) for CAD from June 2012 to May 2014 and who fulfilled the inclusion criteria were enrolled in this prospective registry (**Figure 1**). Patients between 20 and 80 years of age whose LDL cholesterol levels were <120 mg/dl under statin administration or <100 mg/dl under other treatment for dyslipidemia, including lifestyle management, were deemed eligible for inclusion. Stable angina is defined as a clinical syndrome characterized by discomfort in the chest, shoulder, or back, typically elicited by exertion or emotional stress and relieved by rest or nitroglycerin (11). The study exclusion criteria were: 1) PCI for acute coronary syndrome; 2) unsuitable anatomy for VH-IVUS; 3) presented with cardiogenic shock or low left ventricular ejection fraction (<35%); 4) concomitant inflammatory conditions (such as active infection, inflammatory arthritis, or connective tissue disease) or malignancies; and 5) dependence on hemodialysis. Among 70 patients enrolled, 23 were formerly diagnosed as having type 2 DM. The remaining 47 patients, who had not been diagnosed with glucose intolerance, were classified into the following 3 groups, on the

FIGURE 1 Study Population



CGM = continuous glucose monitoring; DM = diabetes mellitus; IGT = impaired glucose tolerance; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; NGT = normal glucose tolerance; PCI = percutaneous coronary intervention; VH-IVUS = virtual histology intravascular ultrasound.

basis of the results of a 75-g OGTT: 1) normal glucose tolerance (NGT), defined as fasting plasma glucose (FPG) level <110 mg/dl and 2-h plasma glucose (PG) level <140 mg/dl (n = 10); 2) impaired glucose tolerance (IGT), defined as FPG level <126 mg/dl and 2-h PG level of 140 to 200 mg/dl (n = 20); and 3) newly diagnosed type 2 DM, defined as FPG level >126 mg/dl or 2-h PG >200 mg/dl (n = 17). We divided the patients into 2 groups according to whether or not they met the DM criteria (DM group and non-DM group). Duration of DM was defined as the time period between the time of diagnosis and the time of examination.

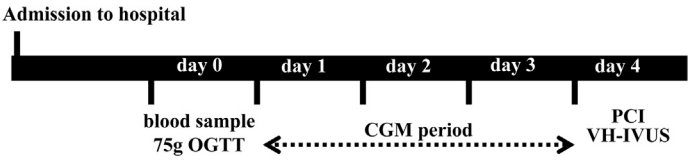
This study was approved by the ethics committee of Kobe University and was carried out according to the guidelines of the Declaration of Helsinki. All enrolled study patients provided their written informed consent for enrollment into the study.

STUDY PROTOCOL. On admission, a blood sample analysis was performed under fasting conditions to evaluate levels of creatinine, glycosylated hemoglobin (HbA1c), total cholesterol, LDL cholesterol, high-density lipoprotein cholesterol, triglycerides, and C-reactive protein (CRP). In addition, a 75-g OGTT was performed in all patients, and levels of PG and immunoreactive insulin were evaluated just before and 30, 60, 90, and 120 min after the oral glucose load.

Subcutaneous interstitial glucose levels were monitored over a period of 3 consecutive days using the CGM System iPro2 (Medtronic, Northridge, California).

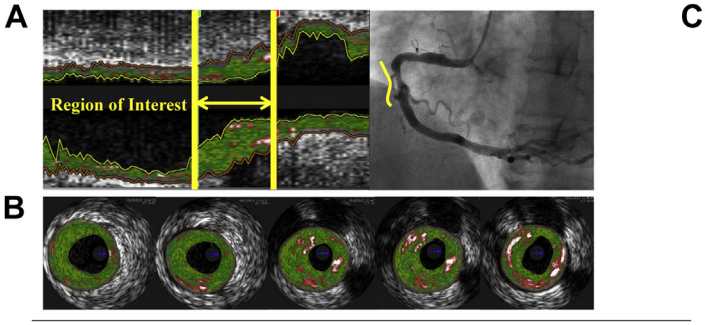
After the CGM examination, all patients underwent a catheterization procedure for PCI to native coronary arteries, and 3 vessels were subjected to VH-IVUS examination (Eagle Eye Platinum 3.5F 20-MHz, Volcano Corp., Rancho Cordova, California). In addition to the culprit lesions for PCI, nonculprit lesions were evaluated with VH-IVUS. Nonculprit lesions were defined as angiographically intermediate lesions (diameter stenosis 30% to 70%) with an IVUS minimum lumen area <4 mm^2 with 50% to 70% plaque burden. The IVUS procedure was performed in a standard fashion, using automated motorized 0.5 mm/s pullback (Figure 2). Culprit lesions were identified by analyzing pre- and inter-crisis

FIGURE 2 Study Protocol

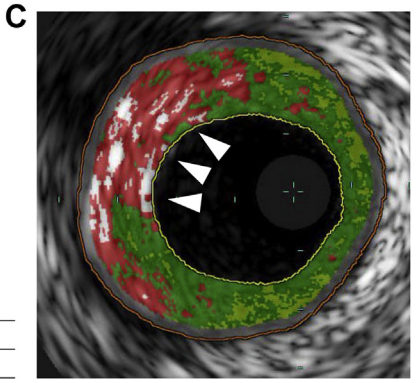


On admission, a blood sample analysis and 75-g oral glucose tolerance test (OGTT) were performed under fasting conditions. Subcutaneous interstitial glucose levels were monitored over a period of 3 consecutive days using CGM. After the CGM examination, 3 vessels were subjected to a VH-IVUS. Abbreviations as in Figure 1.

FIGURE 3 Representative VH-IVUS Images and TCFA



Component	Fibrous	Fibro-fatty	Dense-calcium	Necrotic-core
(%)	56.1	24.1	4.4	15.4



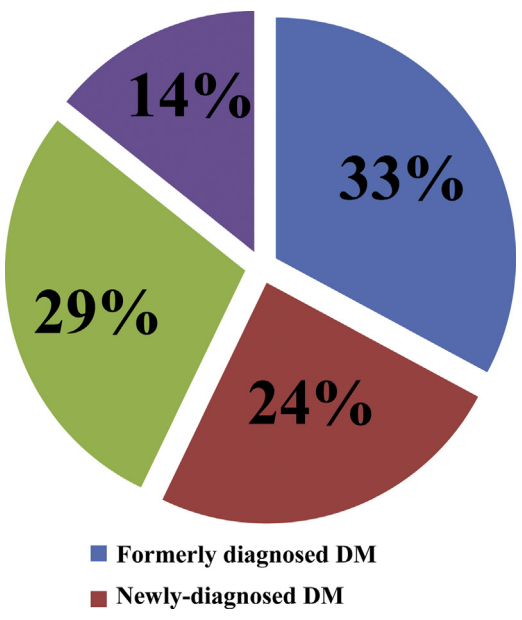
Representative longitudinal virtual histology-intravascular ultrasound (VH-IVUS) images **(A)** and VH-IVUS cross-sectional images along the target area **(B)**. The **table** shows the ratio of each plaque component. **(C)** A representative case of thin-cap fibroatheroma (TCFA). TCFA was defined as a lesion meeting the following criteria: 1) necrotic-core rich lesion (%NC >10%) without evidence of an overlying fibrous component; and 2) % plaque volume >40% in at least 3 consecutive frames by VH-IVUS analysis. **White arrowheads** indicate necrotic core in contact with luminal border.

electrocardiograms, left ventricular wall motion abnormalities, and angiographic lesion appearance.

CGM SYSTEM AND ANALYSIS OF GLUCOSE FLUCTUATION. CGM was performed for 3 consecutive days before PCI, and the daily glucose profile was analyzed using data obtained on days 2 and 3 to avoid any bias due to either insertion or removal of the sensor. In all patients, the CGM analysis software (CareLink iPro, Medtronic, Northridge, California) calculated the median of the variables measured on days 2 and 3: 24-h mean glucose levels, the time in hyperglycemia/hypoglycemia, and the mean amplitude of glycemic excursions (MAGE). MAGE, which was proposed by Service et al. (12), represents fluctuations in blood glucose levels over a 24-h period and was calculated from the daily variations in blood glucose level, measured continuously by CGM over a period of 2 days. Time in hyperglycemia and hypoglycemia were defined as the time when blood glucose levels were >140 and <70 mg/dl, respectively. All patients received optimal meals (25 to 28 kcal/kg of ideal body weight; 60% carbohydrate, 15% to 20% protein, and 20% to 25% fat) during CGM.

IVUS AND VH-IVUS ANALYSIS. Measurements were made of the target vessel, which was defined as the segment from distal to the target lesion to the coronary ostium, evaluating a minimal length of 30 mm. Manual contour detection of both the lumen and the media adventitia interface was performed by 2 experienced analysts (M.K. and H.O.) who were blinded to baseline clinical and angiographic lesion characteristics. We analyzed the whole lesion volume and calculated the lumen, vessel, and plaque (vessel − lumen) volumes using Simpson's method. Interobserver and intraobserver analyses were also performed by these analysts. Intraclass correlation coefficient for interobserver and intraobserver reliabilities of the external elastic membrane volume were 0.952 and 0.968, respectively. VH-IVUS automatically classified the plaque into 4 major components (fibrous [labeled green], fibrofatty [labeled greenish-yellow], necrotic core [NC] [labeled red], and dense calcium [labeled white]) (8). The ratio of each plaque component in both culprit and nonculprit lesions was expressed as a percentage of total plaque volume (**Figures 3A and 3B**). According to the relative amounts of the 4 components, TCFA was defined as a lesion meeting the following criteria: 1) necrotic-core-rich lesion (%NC >10%) without evidence of an overlying fibrous component and; 2) % plaque volume >40% in at least 3 consecutive frames by VH-IVUS analysis (13) (**Figure 3C**). The presence of TCFA required the agreement of 2 independent experienced observers (M.K. and H.O.), and when there was discordance between the observers, a consensus reading was obtained from a third independent reviewer (T.S.). Interobserver and intraobserver agreements for the detection of TCFA were within an acceptable range (interobserver: kappa = 0.927, intraobserver; kappa = 0.887).

FIGURE 4 Classification of Glucose Tolerance



Subjects included 23 formerly diagnosed with DM (33%) **(blue)**, 17 with newly diagnosed DM (24%) **(red)**, 20 patients with IGT (29%) **(green)**, and only 10 with NGT (14%) **(purple)**, totaling to 40 DM and 30 non-DM patients. Abbreviations as in **Figure 1**.

STATISTICAL ANALYSIS. All data are presented as mean ± SD or proportions. Categorical variables were compared using the Fisher exact test and the Student *t* test for continuous variables, as appropriate. Simple linear correlations were calculated using the concept of least squares and by determining the Pearson correlation coefficient, r (* and † represent $p < 0.05$ and $p < 0.001$ for the correlation with % NC, respectively). Linear mixed effect models were used to explore the influence of different variables on the percentage of necrotic core within the plaque and to adjust for covariates. Generalized linear mixed effect models were also used to assess the effect of a set of factors on TCFA. Univariate analysis was first performed, and all variables that satisfied $p < 0.2$ were entered en bloc in the multivariate model, along with age and sex as background variables. In both the linear mixed effect model and generalized linear mixed effect

TABLE 1 Baseline Patient Characteristics

	Overall (n = 70)	DM (n = 40)	Non-DM			p Value DM vs. Non-DM
			All Non-DM (n = 30)	IGT (n = 20)	NGT (n = 10)	
Age, yrs	70.1 ± 10.5	70.3 ± 10.4	70.2 ± 10.7	70.1 ± 11.2	70.3 ± 10.1	0.96
BMI, kg/m^2	24.3 ± 3.3	24.8 ± 3.0	23.5 ± 3.6	24.0 ± 3.4	22.5 ± 4.0	0.09
Male	59 (84)	33 (83)	26 (87)	18 (90)	8 (80)	0.45
Hypertension	53 (76)	31 (78)	22 (73)	14 (70)	8 (80)	0.68
Dyslipidemia	61 (87)	36 (90)	25 (83)	16 (80)	9 (90)	0.32
Smoking	48 (69)	28 (70)	20 (67)	15 (75)	5 (5)	0.76
Current	17 (24)	11 (27)	6 (20)	5 (25)	1 (1)	
Former (quit >3 months)	31 (44)	17 (43)	14 (47)	10 (50)	4 (4)	
Prior myocardial infarction	16 (23)	9 (23)	7 (23)	2 (10)	5 (50)	0.93
Prior PCI	35 (50)	21 (52)	14 (47)	10 (50)	4 (40)	0.63
Prior CABG	1 (1)	0 (0.0)	1 (3)	0 (0)	1 (10)	0.26
Systolic blood pressure, mm Hg	121.6 ± 12.1	121.8 ± 12.9	121.5 ± 11.1	120.6 ± 9.4	123.1 ± 14.1	0.91
Diastolic blood pressure, mm Hg	62.6 ± 7.8	62.0 ± 8.2	63.6 ± 7.2	62.7 ± 7.5	65.2 ± 6.4	0.40
Left ventricular ejection fraction, %	59.6 ± 9.9	60.4 ± 7.7	58.5 ± 12.6	60.0 ± 10.6	55.7 ± 16.1	0.45
Duration of DM, yrs	4.9 ± 9.1	8.5 ± 10.6	–	–	–	–
HbA1c (NGSP) (%)	6.4 ± 0.9	6.8 ± 1.0	5.8 ± 0.3	5.8 ± 0.3	5.7 ± 0.3	<0.001
1,5-AG, μg/ml	15.7 ± 8.0	12.8 ± 6.4	19.5 ± 8.3	19.3 ± 9.4	19.9 ± 6.0	<0.001
Glycoalbumin, %	16.6 ± 3.0	17.7 ± 3.2	15.1 ± 1.7	15.2 ± 1.6	14.8 ± 1.8	<0.001
75-g OGTT						
Fasting PG, mg/dl	103.1 ± 20.9	114.5 ± 22.3	90.2 ± 7.7	91.6 ± 7.8	87.6 ± 7.4	<0.001
2-h PG, mg/dl	213.0 ± 83.6	270.8 ± 71.3	147.4 ± 32.4	165.4 ± 17.8	111.3 ± 23.3	<0.001
Fasting IRI, μU/ml	7.1 ± 5.7	7.7 ± 6.9	6.3 ± 3.8	6.2 ± 3.5	6.5 ± 4.6	0.32
2-h IRI, μU/ml	95.3 ± 94.0	102.1 ± 108.5	87.4 ± 74.6	103.9 ± 84.6	56.2 ± 37.1	0.54
HOMA R	1.9 ± 2.3	2.4 ± 3.0	1.4 ± 0.8	1.4 ± 0.7	1.4 ± 1.0	0.09
HOMA β	73.5 ± 56.4	58.1 ± 37.7	91.0 ± 68.5	87.3 ± 65.2	98.4 ± 77.8	0.024
Total cholesterol, mg/dl	155.0 ± 26.8	154.4 ± 27.4	155.3 ± 26.6	149.8 ± 25.1	166.4 ± 27.3	0.94
LDL cholesterol, mg/dl	87.8 ± 18.7	88.1 ± 20.1	87.4 ± 17.0	85.6 ± 17.9	91.1 ± 15.1	0.88
HDL cholesterol, mg/dl	46.0 ± 12.0	44.1 ± 10.9	48.4 ± 13.1	47.5 ± 13.2	50.4 ± 13.3	0.14
Triglyceride, mg/dl	128.5 ± 60.6	140.1 ± 57.7	113.7 ± 62.0	113.0 ± 69.8	115.3 ± 45.9	0.07
CRP, mg/dl	0.17 ± 0.28	0.14 ± 0.22	0.20 ± 0.34	0.26 ± 0.40	0.10 ± 0.11	0.39
Creatinine, mg/dl	0.98 ± 0.32	1.03 ± 0.36	0.93 ± 0.24	0.91 ± 0.20	0.97 ± 0.31	0.20
Medication on admission						
Aspirin	58 (83)	34 (85)	24 (80)	18 (90)	6 (60)	0.32
Thienopyridine	32 (46)	20 (50)	12 (40)	8 (40)	4 (40)	0.35
Statin	53 (76)	32 (80)	21 (70)	13 (65)	8 (80)	0.33
EPA	3 (4)	2 (13)	1 (3)	1 (5)	0 (0.0)	0.61
Ezetimibe	6 (9)	5 (13)	1 (3)	1 (5)	0 (0.0)	0.18
Fibrate	2 (3)	1 (3)	1 (3)	1 (5)	0 (0.0)	0.68
ACE-I/ARB	44 (63)	26 (67)	18 (60)	13 (65)	5 (50)	0.57
Beta-blocker	30 (43)	19 (22)	11 (37)	8 (40)	3 (30)	0.32
Insulin	4 (6)	4 (10)				
Metformin	6 (9)	6 (15)				
SU	13 (19)	13 (33)				
α-GI	4 (6)	4 (10)				
Glinide	0 (0)	0 (0)				
Pioglitazone	0 (0)	0 (0)				
DPP4-I	16 (23)	16 (40)				

Values are mean ± SD or n (%).

1,5 AG = 1,5 anhydroglucitol; α-GI = α-glucosidase inhibitor; ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; CABG = coronary artery bypass graft; CRP = C-reactive protein; DM = diabetes mellitus; DPP4-I = dipeptidyl peptidase-4 inhibitor EPA = eicosapentaenoic acid; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; HOMA B = homeostasis model assessment beta; HOMA R = homeostasis model assessment ratio; IGT = impaired glucose tolerance; IRI = immunoreactive insulin; LDL = low-density lipoprotein; NGT = normal glucose tolerance; OGTT = oral glucose tolerance test; PCI = percutaneous coronary intervention; PG = plasma glucose; SU = sulfonylurea.

TABLE 2 Variables Measured by the Continuous Glucose Monitoring System

	Overall (n = 70)	DM (n = 40)	Non-DM			p Value DM vs. Non-DM
			All Non-DM (n = 30)	IGT (n = 20)	NGT (n = 10)	
MAGE, mg/dl	72.7 ± 35.1	82.1 ± 34.1	60.1 ± 32.9	63.6 ± 32.9	52.8 ± 33.6	0.008
Mean BG, mg/dl	134.7 ± 29.0	149.4 ± 30.7	115.5 ± 8.5	117.1 ± 7.8	112.4 ± 9.5	<0.001
Max BG, mg/dl	216.3 ± 49.6	238.4 ± 48.7	187.5 ± 33.8	190.2 ± 31.4	182.2 ± 39.3	<0.001
Min BG, mg/dl	78.0 ± 28.4	85.7 ± 32.4	67.8 ± 18.0	69.9 ± 18.5	63.8 ± 17.1	0.005
Time in hyperglycemia, h	26.2 ± 25.7	39.3 ± 27.2	9.1 ± 6.8	10.6 ± 6.6	5.7 ± 6.1	<0.001
Time in hypoglycemia, h	1.3 ± 2.6	0.8 ± 1.7	2.0 ± 3.4	2.1 ± 3.9	1.7 ± 2.0	0.094

Values are mean ± SD. Time in hyperglycemia was defined as the time when blood glucose levels were above 140 mg/dl. Time in hypoglycemia was defined as the time when blood glucose levels were under 70 mg/dl.

BG = blood glucose; MAGE = mean amplitude of glycemic excursion; other abbreviations as in Table 1.

model, patients were treated as random effect variables. To assess the interobserver and intraobserver variability, the results were compared with the kappa test of concordance to the categorical data, and a Bland-Altman plot was fulfilled for continuous data. Analyses were performed using commercially available software (SPSS version 22, IBM Corp., Armonk, New York). Values of $p < 0.05$ were considered statistically significant.

RESULTS

BASELINE PATIENT CHARACTERISTICS. Between June 2012 and May 2014, a total of 70 patients were enrolled (Figure 4). Baseline patient characteristics and medications on admission are shown in Table 1. No significant differences between the DM and non-DM groups were observed in the baseline characteristics, except for glycemic variables such as HbA1c,

TABLE 3 Plaque Characteristics Evaluated by VH-IVUS

Plaque Analysis	Overall (n = 165)	DM (n = 100)	Non-DM			p Value DM vs. Non-DM
			All Non-DM (n = 65)	IGT (n = 48)	NGT (n = 17)	
Culprit lesion	55 (33)	37 (37)	18 (28)	12 (25)	6 (35)	0.21
Plaque location						0.90
LAD	53 (32)	35 (35)	18 (27)	13 (27)	5 (29)	
LCx	55 (33)	33 (33)	22 (34)	16 (33)	6 (35)	
RCA	50 (30)	27 (27)	23 (35)	17 (35)	6 (35)	
LMT	7 (4)	5 (5)	2 (3)	2 (4)	0 (0)	
Plaque volume						
Absolute data, mm^3	107.6 ± 73.3	107.7 ± 68.5	107.3 ± 80.5	116.4 ± 86.2	81.4 ± 55.9	0.97
Plaque burden, %	56.5 ± 8.8	56.8 ± 8.8	56.1 ± 8.9	56.5 ± 8.9	54.5 ± 9.0	0.63
Lesion length, mm	14.2 ± 8.3	14.2 ± 8.3	14.3 ± 8.2	14.7 ± 8.5	13.2 ± 7.4	0.87
Fibrous						
Absolute data, mm^3	40.2 ± 32.4	40.2 ± 29.6	40.2 ± 36.5	44.4 ± 39.6	28.2 ± 22.9	0.99
Relative data, %	59.1 ± 8.9	58.1 ± 9.2	60.7 ± 8.2	60.4 ± 7.8	61.4 ± 9.6	0.070
Fibrofatty						
Absolute data, mm^3	9.1 ± 8.3	8.8 ± 7.9	9.6 ± 8.9	10.4 ± 9.8	7.0 ± 5.7	0.57
Relative data, %	13.4 ± 7.4	12.7 ± 7.4	14.4 ± 7.3	13.8 ± 6.6	16.1 ± 8.9	0.15
Dense-calcium						
Absolute data, mm^3	5.4 ± 5.5	5.7 ± 5.6	4.8 ± 5.2	5.3 ± 5.5	3.2 ± 3.8	0.27
Relative data, %	8.1 ± 6.3	8.7 ± 6.8	7.1 ± 5.2	7.2 ± 4.9	6.8 ± 6.3	0.086
Necrotic core						
Absolute data, mm^3	13.9 ± 12.8	14.6 ± 11.9	12.9 ± 14.1	14.5 ± 15.0	8.4 ± 9.9	0.41
Relative data, %	19.3 ± 5.9	20.4 ± 5.5	17.7 ± 6.3	18.5 ± 5.9	15.6 ± 7.1	0.004
Thin-cap fibroatheromas	15 (9)	13 (13)	2 (3)	2 (4)	0 (0)	0.030

Values are n (%) or mean ± SD.

LAD = left anterior descending artery; LCx = left circumflex artery; LMT = left main trunk; RCA = right coronary artery; other abbreviations as in Table 1.

TABLE 4 Pearson Correlation Coefficients

	Overall	DM	Non-DM
Fasting PG	0.172*	0.127	−0.077
OGTT 2-h PG	0.242†	0.121	0.276*
Fasting IRI	0.027	−0.005	0.017
OGTT 2-h IRI	−0.080	−0.097	−0.080
MAGE	0.490†	0.410†	0.511†
Mean BG by CGM	0.337†	0.376†	−0.066
Time in hyperglycemia	0.285†	0.266†	0.176
Time in hypoglycemia	0.184*	−0.035	0.416†
HbA1c	0.276†	0.230*	0.148
1,5 AG	−0.275†	−0.275†	−0.101
Glycoalbumin	0.302†	0.260*	0.102
Duration of DM	0.233†	0.205*	–
HOMA-R	0.046	0.005	0.006
HOMA-β	−0.091	−0.156	0.053
HDL cholesterol	−0.069	0.037	−0.113
LDL cholesterol	0.035	−0.008	0.106
TG	−0.042	−0.198	0.059
CRP	0.122	−0.024	0.308*
Creatinine	0.002	−0.056	0.005
Age	−0.125	−0.172	−0.064
BMI	0.091	−0.016	0.153
Systolic blood pressure	−0.088	−0.018	−0.027
Diastolic blood pressure	0.074	0.102	0.082

Values are r values. Association between the percentage of necrotic core within the plaque and clinical and laboratory variables. *$p < 0.05$, †$p < 0.001$.

Abbreviations as in Tables 1 and 2.

1,5-AG, and glycoalbumin levels. According to the 75-g OGTT data, FPG and 2-h PG levels were significantly higher in the DM group than in the non-DM group. Medications on admission did not differ between the 2 groups, except for diabetes drug usage.

The variables measured by CGM are summarized in Table 2. All variables had significantly greater values in the DM group than in the non-DM group, except that the time in hypoglycemia tended to be longer in the non-DM group than in DM group.

TABLE 5 Linear Mixed Effect Model Adjusted With Confounders

	Coefficients			
	B	SE	t	p Value
All patients (n = 165)				
MAGE	0.080	0.020	3.930	<0.001
Duration of DM	0.146	0.097	1.505	0.140
DM patients (n = 100)				
MAGE	0.054	0.027	1.981	0.060
Duration of DM	0.132	0.098	1.354	0.191
Non-DM patients (n = 65)				
MAGE	0.135	0.035	3.905	0.001

The percentage of necrotic core within the plaque is the dependent variable. All models were adjusted by age, sex, HbA1c, fasting PG, 1,5-AG, glycoalbumin, and 2-h PG.

Abbreviations as in Tables 1 and 2.

PLAQUE CHARACTERISTICS OBTAINED BY IVUS. A total of 165 plaques were identified in 70 patients: 100 plaques in 40 DM patients (2.5 plaques/patient) and 65 plaques in 30 non-DM patients (2.2 plaques/patient); 33% of plaques were in the culprit lesion. A total of 30 patients underwent a 3-vessel IVUS examination, whereas the remaining 40 patients underwent a 1- or 2-vessel IVUS examination. The plaque characteristics are shown in Table 3. The %NC was significantly higher in the DM group than in the non-DM group, whereas the percentage of fibrous component tended to be lower in the DM group. Compared with plaques in the non-DM group, those in the DM group had a significantly higher incidence of TCFA (13% vs. 2%, $p = 0.030$).

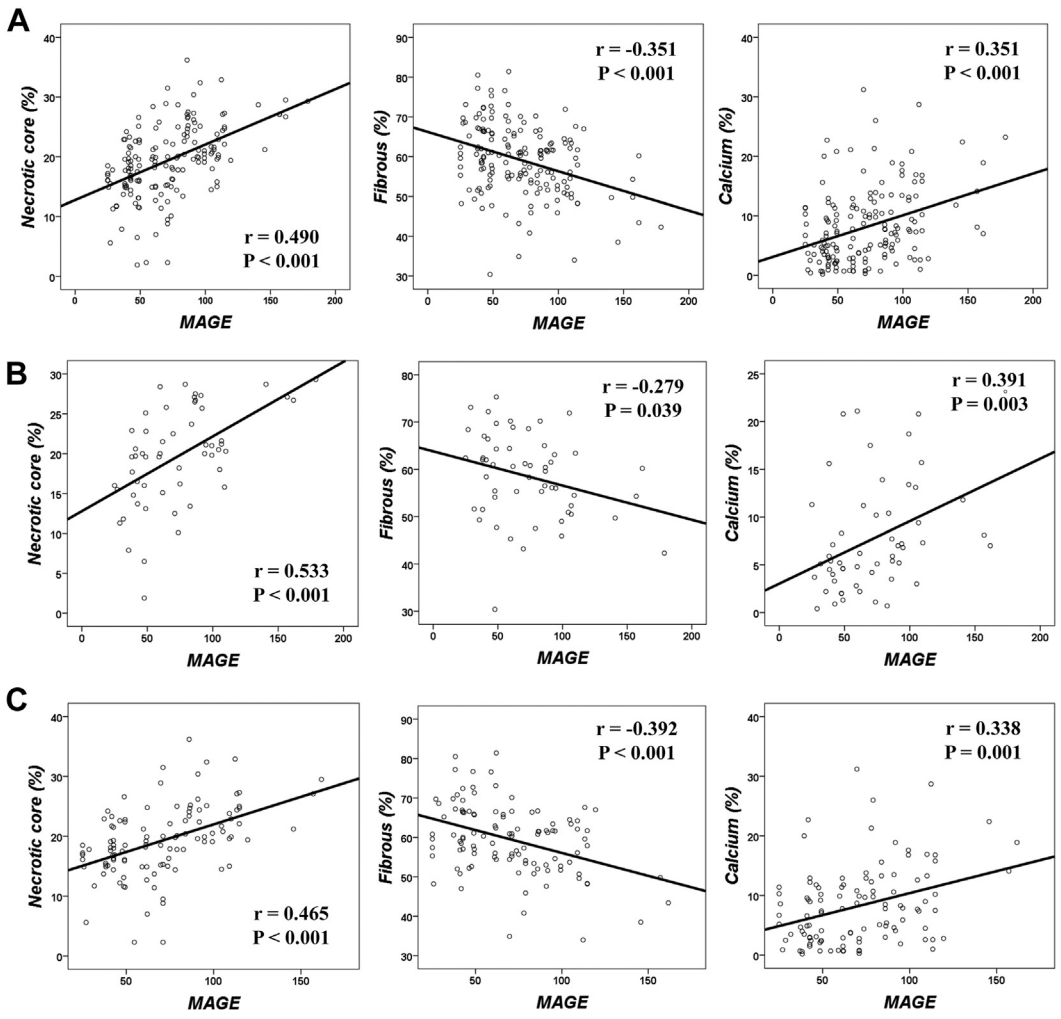
RELATIONSHIPS BETWEEN %NC AND CLINICAL AND LABORATORY VARIABLES. The %NC was tested for simple linear correlations against markers of glucose control and other laboratory variables (Table 4). In all patients, the strongest correlation was found between %NC and MAGE ($r = 0.490$; $p < 0.001$). In contrast, clinical and laboratory data other than glycemic variables were not correlated with %NC. When analyzed separately, in both the DM and non-DM groups, the strongest correlation was found with MAGE ($r = 0.410$, $p < 0.001$; and $r = 0.511$, $p < 0.001$, respectively). In non-DM patients, the time in hypoglycemia and CRP level were significantly correlated with %NC.

The linear mixed effect model adjusted with confounders was used to assess the independent effects of diabetic parameters on %NC (Table 5). In the entire patient population, multivariate analysis demonstrated that a larger MAGE was significantly associated with a higher %NC, whereas a longer duration of DM had a tendency toward a higher %NC. In the non-DM group, a larger MAGE was the only independent predictor of a higher %NC.

RELATIONSHIPS BETWEEN MAGE AND COMPONENTS WITHIN THE PLAQUE. MAGE was assessed for simple linear correlations with other components within the plaque. The percentage of fibrous component had a negative correlation, whereas the percentage of calcium had a positive correlation both in culprit and nonculprit lesions (Figures 5A to 5C). The correlation coefficient between %NC and MAGE in culprit lesions was numerically higher than that in nonculprit lesions ($r = 0.533$ vs. $r = 0.465$, respectively).

In addition, the correlation with MAGE and %NC was assessed in DM, IGT, and NGT patients (Figure 6). In DM, IGT, and NGT patients, MAGE had a significant positive correlation with %NC.

FIGURE 5 The Correlation Between MAGE and Plaque Component



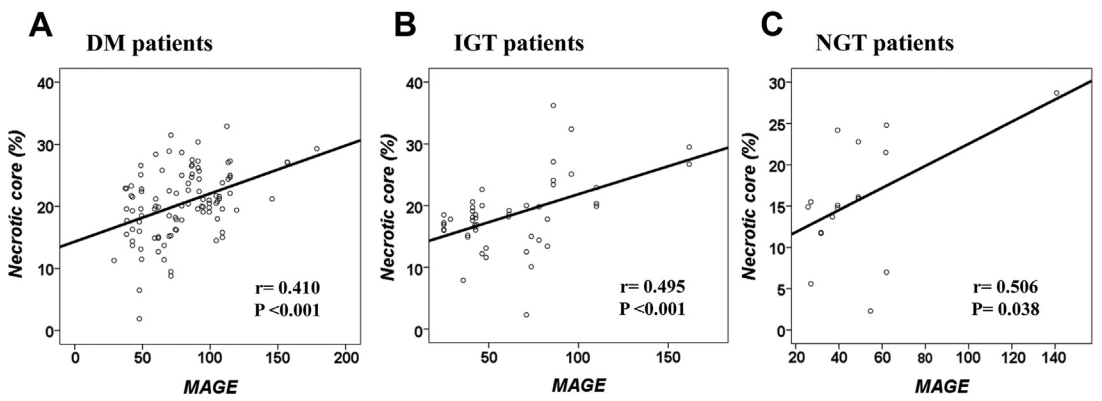
The correlation between mean amplitude of glycemic excursion (MAGE) and the percentage of **(left)** necrotic core, **(middle)** fibrous component, and **(right)** calcium in **(A)** all plaques, **(B)** culprit plaques, and **(C)** nonculprit plaques.

ASSOCIATIONS BETWEEN TCFA AND CLINICAL AND LABORATORY VARIABLES. Generalized linear mixed effect model was applied to identify independent risk factors for TCFA (Table 6). Univariate analysis was first conducted to identify potential factors for TCFA. All variables with $p < 0.2$ on univariate analysis were tested by multivariate analysis. In all plaques, MAGE was the only independent predictor of TCFA (odds ratio: 1.037; 95% confidence interval: 1.010 to 1.065; $p = 0.007$).

DISCUSSION

The current study represents an in vivo report to investigate the effect of glucose fluctuations on coronary plaque properties in patients with CAD who are under statin administration or other medical management of dyslipidemia. The main findings of this study can be summarized as follows: 1) among patients with CAD referred for PCI under treatment for dyslipidemia, 86% of the subjects presented with glucose intolerance, including newly and formerly diagnosed DM and IGT; 2) in all patients with CAD who are under treatment for dyslipidemia, glucose fluctuation is an important contributing factor to the distribution of plaque components; and 3) a large glucose fluctuation is the only independent risk factor for the progression of necrotic core within the coronary plaque and formation of TCFA.

FIGURE 6 The Correlation Between MAGE and %NC



This figure shows the correlation between mean amplitude of glycemic excursion (MAGE) and volume percentage of necrotic core within the plaque (%NC) in **(A)** DM, **(B)** IGT, and **(C)** NGT. Abbreviations as in **Figure 1**.

GLUCOSE INTOLERANCE AND PROGRESSION OF CAD. It is well known that DM patients form a high-risk category among patients with CAD, and the prevalence of diabetes has recently been increasing worldwide. Thus, glucose intolerance has emerged as an important residual risk for CAD development. Although a longer DM duration has been associated with the progression of coronary plaque vulnerability (14), even in the early stage of IGT, the progression of CAD has already started and affects the patient outcomes (15). Recently, it has been reported that glucose fluctuation, such as hypoglycemia and post-prandial hyperglycemia, arises from an early stage of glucose intolerance and may be an important contributing factor to the development of CAD as a residual risk, apart from dyslipidemia (3,5). In this study, the longer time in hypoglycemia and higher CRP level was significantly associated with the higher %NC in the non-DM patients, suggesting that from the early stage of glucose intolerance, hypoglycemia may cause inflammation and result in the development of plaque vulnerability.

THE RELATIONSHIP BETWEEN GLUCOSE FLUCTUATION AND CORONARY PLAQUE PROPERTIES. The present study showed that glucose fluctuation had a stronger positive correlation with %NC than with the duration of DM in DM patients. Moreover, multivariate analysis revealed that glucose fluctuation was independently associated with the formation of NC in non-DM patients. Previous investigators have suggested that a large glucose fluctuation by CGM is associated with endothelial dysfunction (16,17). Monnier et al. (16) reported that, by evaluating the correlation between oxidative stress estimated from 24-h urinary excretion rates of free 8-iso prostaglandin F2 and glucose fluctuation obtained from CGM, glucose fluctuations exhibited a more specific triggering effect on oxidative stress than did chronic sustained hyperglycemia. In addition, Risso et al. (18) explored the effect of fluctuating glucose on endothelial cells. The investigators determined that apoptosis was enhanced in human umbilical vein endothelial cells exposed to intermittent, rather than constant, high glucose concentration. These investigations suggested that daily glucose fluctuation could have a powerful effect on the promotion of plaque vulnerability, as observed in this study.

THE RELATIONSHIP BETWEEN GLUCOSE FLUCTUATION AND TCFA. Previous studies demonstrated that, compared with non-DM patients, DM patients had a higher proportion of NC and calcium within the plaque and a greater presence of TCFA by VH-IVUS analysis, which is a surrogate marker of unstable coronary plaque and future coronary events (14). A recent report suggests that a large glucose fluctuation is associated with the progression of atherosclerosis, leading to an ACS (19). The present study demonstrated that a large glucose fluctuation had an effect on the formation of TCFA in all subjects.

TABLE 6 Generalized Linear Mixed Effect Model Adjusted With Confounders for Determinants of TCFA

Variables	Univariate			Multivariate		
	OR	95% CI	p Value	OR	95% CI	p Value
MAGE	1.029	1.004–1.054	0.021	1.037	1.010–1.065	0.007
DM	5.669	0.852–37.738	0.073			
Time in hyperglycemia (h)	1.027	0.998–1.057	0.069			

This multivariate model was adjusted by age, sex, DM, and time in hyperglycemia.
CI = confidence interval; OR = odds ratio; other abbreviations as in **Tables 1 and 2**.

A dramatic glucose fluctuation, especially hypoglycemia, induced the activation of the sympathetic nervous system (20), followed by elevated blood pressure and vasoconstriction. As a result, these phenomena might cause the progression of vulnerable plaque, characterized by TCFA (21).

Several observational studies reported that the strict control of diabetes at an earlier stage helps to prevent macroangiopathy (22), suggesting a need for the earlier diagnosis and treatment of diabetes and glucose intolerance. The present study demonstrated that the percentage of fibrous component had a negative correlation with MAGE, whereas the percentage of calcium had a positive correlation. This suggests that the control of glucose fluctuation may be beneficial to prevent the formation of TCFA or to stabilize vulnerable plaque. A large-scale prospective study is warranted to evaluate whether additional glucose fluctuation control will decrease the progression of TCFA and late clinical events.

STUDY LIMITATIONS. First, this was a single-center study with a relatively small number of patients; thus, there was a potential risk of patient selection bias. Second, we only assessed patients with stable angina pectoris. We excluded ACS patients from this study because this population was highly heterogeneous with multiple confounding factors, such as uncontrolled dyslipidemia, stress hyperglycemia, and drastic changes in diet and medications after admission. Further study is warranted including ACS patients, because, as vulnerable plaques are more frequently found, they might be a better target to address the influence of MAGE on plaque characteristics. Third, we did not validate the VH-IVUS data with histological findings; therefore, the regions identified as VH-TCFA were not confirmed to contain a large necrotic core overlapping with a thin cap. However, there are no 1-on-1 VH-IVUS criteria that have been validated with histological findings for the identification of TCFA. Moreover, the ability of VH-IVUS to identify lipidic components accurately has been validated previously (23). Therefore, the information obtained in this study seems to be valid, but a pathological validation of VH-IVUS-based criteria for the identification of TCFA is warranted to further confirm these results. Fourth, we excluded patients whose LDL cholesterol level was >120 mg/dl under statin treatment or >100 mg/dl without statins, and included only patients who were thought to be well controlled in the treatment of dyslipidemia. A previous report suggested %NC was strongly influenced by the plasma level of LDL (24). To reduce the influence of the lipid profile, we excluded patients with uncontrolled lipid levels. To explore the direct effect of glucose fluctuation on coronary vulnerability, further study is warranted to include only patients with more strictly controlled dyslipidemia; that is, LDL <70 mg/dl. Finally, there might be a potential interaction among DM, MAGE, and %NC because HbA1c, a marker of averaged blood glucose level, MAGE, and %NC were higher compared with levels in non-DM patients. However, the correlation coefficient between HbA1c and MAGE was very poor in DM patients ($r = 0.22$), and no correlation was found in non-DM patients. This suggests that a high level of average blood glucose does not always indicate high MAGE. The result of multivariate analysis that higher MAGE was the independent predictor of %NC is of scientific value.

CONCLUSIONS

Daily glucose fluctuations may have an effect on coronary plaque vulnerability in patients with CAD pretreated with lipid-lowering therapy, marking glucose fluctuation as an important target for management, apart from the control of dyslipidemia. Further investigations should address the rationale of early detection and control of glucose fluctuation in the era of the universal use of statins for CAD patients.

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Toshiro Shinke, Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan. E-mail: shinke@med.kobe-u.ac.jp.

PERSPECTIVES

WHAT IS KNOWN? Beyond dyslipidemia management, large glucose fluctuation, such as postprandial hyperglycemia, may lead to adverse clinical events in CAD. However, mechanisms for its deteriorative effects are unknown.

WHAT IS NEW? Mean amplitude of glycemic excursion, representing daily glucose fluctuation, was strongly associated with the progression of vulnerable coronary lesions even under adequate lipid-lowering therapy.

WHAT IS NEXT? Whether early detection and management of glucose fluctuation could stabilize coronary lesions and improve clinical outcome should be addressed in large-scale clinical trials.

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KEY WORDS continuous glucose monitoring, glucose fluctuation, mean amplitude of glycemic excursion, thin-cap fibroatheroma, virtual histology intravascular ultrasound